

DIABETIC KERATOPATHY*

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ISOLATED AND SOMETIMES CONFLICTING REPORTS OF CORNEAL AND ANTERIOR SEGMENT abnormalities in patients with diabetes mellitus have appeared in the world literature for many decades. Francois¹ recalled observations, known as early as 1858, which indicated that wound healing is delayed and there is an increased risk of infection in diabetic patients. Other authors have described decreased tear production,² reduced corneal sensation,³ neurotrophic corneal ulcers,⁴ the presence of glucose in tears,⁵ wrinkling of Descemet's membrane,⁶ and a characteristic epithelial keratodystrophy⁷ which was reported to occur in approximately one-third of all diabetic patients. In 1967 Collier⁸ published a comprehensive review of corneal pathology in diabetes. He emphasized the importance of determining whether pathognomonic forms of keratopathy existed, and if so, whether one or more of these entities might serve as an early diagnostic sign of the disease.

Recently, and specifically with the advent of vitreous surgery in diabetic patients, attention has focused on corneal epithelium, its basement membrane, and a delay in corneal reepithelialization following surgical trauma.⁹ In 1978, a preliminary report by Kenyon¹⁰ described a thickened and multilaminar structure of the epithelial basement membrane in the corneas of diabetic patients. Specimens examined were obtained from scraping the epithelium in patients undergoing vitreo-retinal surgery. If distinct abnormalities exist in epithelial basement membrane, this could

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TABLE I: ANTERIOR SEGMENT EVALUATION FOR PATIENTS WITH DIABETES MELLITUS

Diabetic History
General Ophthalmic History
Culture for Bacteria and Fungi
Bromicroscopy of Cornea
Pachymetry
Corneal Staining with Rose Bengal and Fluorescein
Corneal Sensitivity (Luneau-Coffignon Anesthesiometer)
Schirmer (Basic and Reflex Secretion)
Semiquantitative Tear Glucose Determination
Specular Microscopy

explain some of the observations noted following surgical trauma, and such abnormalities might also relate to the reported forms of keratopathy.

The purpose of this paper is to describe clinical observations noted in a random population of diabetic patients examined over a two year period of time; and to determine whether specific corneal abnormalities exist in diabetes mellitus. Patients for this study were obtained from our metabolic clinics and did not represent patients selected from a population known to have ocular disease or ocular symptoms.

METHODS

Initial examinations were completed for 120 patients and 89 patients from this group were re-examined approximately one year later. Clinical evaluations consisted of the items listed in Table I. Patients were subdivided into adult onset diabetes (AODM) and juvenile onset disease (JODM) according to the following criteria:* *JODM*: These patients had rapid onset of their disease usually occurring prior to age 25 years; they were insulin dependent and showed propensity for ketosis. *AODM*: A disease characterized by gradual onset usually after age 25 years; the patients may or may not require insulin, but often there is a history of progression from control by diet alone to oral hypoglycemic agents and eventual insulin

*A classification of diabetes and other categories of glucose intolerance has been developed by the international work group sponsored by the National Diabetes Data Group of the National Institutes of Health. This group recommends that nomenclature for this disease be changed to: Type I or insulin dependent diabetes mellitus (IDDM) and Type II or noninsulin dependent diabetes mellitus (NIDDM) to replace the designation JODM and AODM respectively. This recommendation is an attempt to reflect the heterogeneity of the disease and to deemphasize age of onset. The designations JODM and AODM used in this paper adhere to the recommended criteria established for Type I and Type II classifications.¹¹

supplementation. In general these patients were not prone to develop ketosis.

Diabetic Control: Fasting blood sugars as well as hemoglobin A-1_c determinations were used to designate good, fair, and poor metabolic control. The definitions of metabolic control are as follows:

Good Control:

Glycohemoglobin level of 4.4% to 8.2% and a fasting blood sugar (FBS) level of less than 150 mg%.

Fair Control:

Glycohemoglobin level of 8.3% to 9.2% and FBS levels less than 250 mg%.

Poor Control:

Glycohemoglobin level of greater than 9.2% and FBS levels greater than 250 mg%.

The hemoglobin A-1_c determinations were performed according to the method of Trivelli.¹²

Semiquantitative measurements of tear production were determined by using standard Schirmer paper strips placed at or near the punctum for five minutes. One hour later a strip was placed in the same location following two drops of topical benoxinate hydrochloride (Dorsacaine®). Reduced tear production was defined as wetting of less than 11 mm of the paper strips. Measurements of tear glucose were determined by placing the wet Schirmer strip on Diastix® test strip. The Diastix strip was read according to a standard colorimetric scale.

Corneal sensation was determined by use of the Luneau-Coffignon anesthesiometer with the patient in a supine position. The filament was initially set at a scale reading of 6 cm and retracted in ½ cm decrements. The point at which the patient responded was then recorded.

Cultures for microorganisms were obtained from the lid margins and conjunctival cul-de-sac utilizing a Calgiswab® in heart-brain infusion mixture. The swab sticks were placed directly onto blood agar, chocolate agar, and sabarose media. The swab used for lid margin cultures was placed in thioglycollate broth for subsequent anaerobic cultures.

Corneal endothelial cell counts were determined from photographs obtained with a Heyer-Schulte HS-CEM3 contact system. Endothelial cells were counted according to the method described by Schutten.¹³ Corneal thickness measurements were determined by use of a Haag-Streit pachymeter as modified by Mishima.¹⁴

Tissue prepared for electron microscopy was fixed in glutaraldehyde and osmium; sectioned with a diamond knife, and examined by use of an RCA-MU4 transmission electron microscope.

TABLE II: AGE DISTRIBUTION VERSUS DURATION OF DISEASE IN ADULT ONSET AND JUVENILE ONSET DIABETES MELLITUS

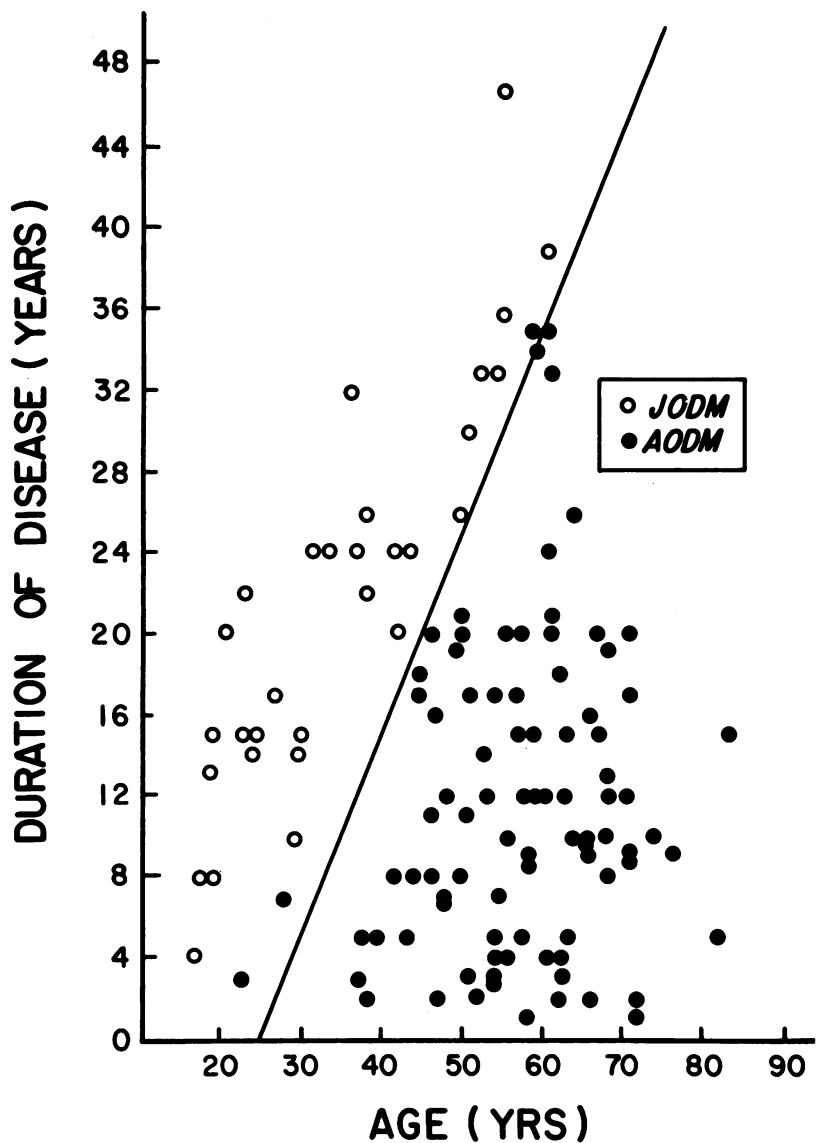


TABLE III: FAMILY HISTORY OF DIABETES IN AODM vs JODM (CLOSEST RELATIVE)						
	FIRST DEGREE		SECOND DEGREE		NO FAMILY	Hx.
AODM:	62/90	69%	6/90	7%	22/90	24%
JODM:	10/29	34%	9/29	31%	10/29	35%

TABLE IV: PRESENCE OF CORNEAL EPITHELIAL KERATOPATHY IN DIABETES MELLITUS						
	MALE		FEMALE		ALL PATIENTS	
AODM	16/23	70%	32/47	68%	48/70	69%
JODM	6/11	54%	3/8	38%	9/19	47%
TOTAL	22/34	65%	35/55	64%	57/89	64%

Sorbitol determinations were measured from corneal epithelial scrapings using the gas liquid chromatography technique described by Sweeley.¹⁵

RESULTS

Table II indicates the age of patients with regard to the duration and classification of their disease. Table III indicates the family history of diabetes in both the AODM and JODM groups of patients based on their closest relative. With regard to the existence of a specific or pathognomonic form of keratopathy, we observed that corneal epithelial lesions were present in 64% of patients examined during the second year of the study (Table IV), and 47% of those patients examined in the first year of the study. This variation in prevalence is probably explained by the

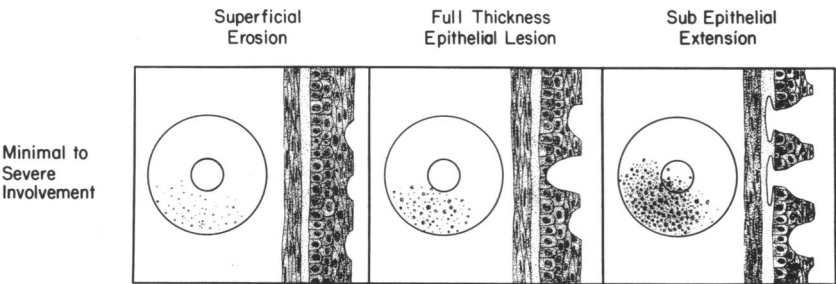


FIGURE 1
Diagrammatic representation of the extent and depth of corneal epithelial lesions found in patients with diabetes mellitus.

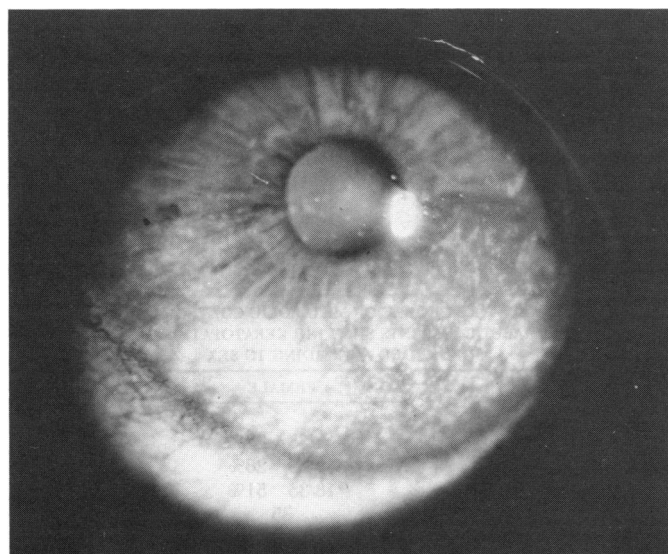
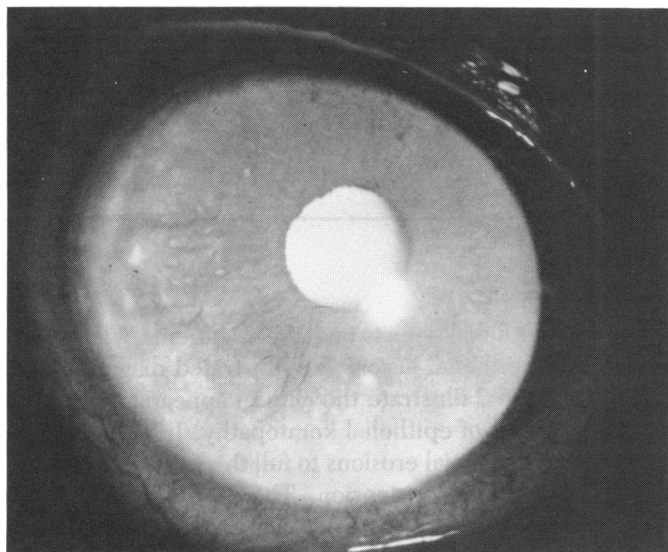


FIGURE 2 & 3

Representative corneal epithelial defects found in diabetic patients; ranging from minimal to extensive involvement (stained with fluorescein).

TABLE V: DEGREE OF METABOLIC CONTROL IN DIABETIC PATIENTS WHO SHOW CORNEAL EPITHELIAL KERATOPATHY

	MALE		FEMALE		ALL PATIENTS	
AODM						
Good:	5/17	29%	10/31	32%	15/48	31%
Fair:	7/17	42%	6/31	19%	13/48	27%
Poor:	5/17	29%	15/31	49%	20/48	42%
TOTAL	17		31		48	

transient nature of epithelial defects in diabetic patients. Variations in the extent and depth of epithelial lesions are illustrated diagrammatically in Figure 1. Figures 2 and 3 illustrate the clinical appearance of both minimal and advanced forms of epithelial keratopathy. In general, epithelial defects ranged from superficial erosions to full thickness epithelial lesions; with occasional subepithelial extension. The lesions were located predominantly in the lower one-third to one-half of the cornea, and stained variably with fluorescein depending upon the depth of the defects.

This form of epithelial keratopathy was more common in adult onset disease (69%) compared to juvenile onset disease (47%), (Table IV). The average age of patients was, of course, significantly greater in the adult onset group but the duration of disease was in some cases greater in the juvenile onset group (Table II). If one combines the AODM and JODM groups, there were equivalent percentages of involved individuals in both sexes (Table IV). The data in Table V indicates the keratopathy was not related to the degree of diabetic control unless one subdivides these patients according to sex and type of diabetes, ie, it appears that female

TABLE VI: DEGREE OF METABOLIC CONTROL IN DIABETIC PATIENTS SHOWING KERATOPATHY — SUBDIVIDED ACCORDING TO SEX

	FEMALE	
AODM		
Good:	8/35	23%
Fair:	9/35	26%
Poor:	18/35	51%
TOTAL	35	
JODM		
Good:	0/11	
Fair:	1/11	9%
Poor:	10/11	91%
TOTAL	11	

TABLE VII: CORNEAL THICKNESS MEASUREMENTS IN DIABETIC PATIENTS ACCORDING TO DISEASE TYPE

	NORMAL		INCREASED		TOTAL
AODM	40/70	57%	30/70	43%	70
JODM	15/19	79%	4/19	21%	19
TOTAL	55/89	62%	3/89	38%	89

diabetic patients under poor metabolic control have a higher prevalence of keratopathy; and this predilection may be enhanced in the juvenile onset group (Table VI). While a significant percentage of patients in this study showed an increase in corneal thickness above 0.55 mm (Table VII), this increase did not correlate with the presence of keratopathy (Table VIII).

Measurements of tear production and corneal sensation indicated that 47% of eyes (82 of 175) had decreased tear production, and within this group 23% of eyes (19 of 82) showed reduced corneal sensation (Table IX). In the entire group of patients, corneal sensation was reduced in 18% of eyes (32 of 175), (Table IX). Correlation between decreased corneal sensation and the presence of peripheral neuropathy will be the subject of a separate publication, but preliminary results suggest that corneal hypoesthesia is part of a generalized polyneuropathy. The tears of all patients were examined for the presence of glucose and data analysis shows that approximately 58% of patients revealed some glucose in their tears even during a fasting state where the average blood glucose level was 219 mg%.

Cultures for bacterial and mycotic organisms were obtained from all patients in this study. This was done because of the common belief that diabetic patients are more subject to infection. In addition, the observed keratopathy is not inconsistent with that seen in staphylococcal keratoconjunctivitis. The presence of glucose in tears might also be expected to alter the types of microorganisms which inhabit the conjunctival cul-

TABLE VIII: KERATOPATHY IN DIABETIC PATIENTS RELATED TO CORNEAL THICKNESS MEASUREMENTS

	NORMAL THICK.		INCREASED THICK.	
AODM w/o keratopathy:	26/45	58%	19/45	42%
AODM with keratopathy:	30/45	67%	15/45	33%
JODM w/o keratopathy:	12/18	67%	6/18	33%
JODM with keratopathy:	6/12	50%	6/12	50%

TABLE IX: MEASUREMENTS OF TEAR PRODUCTION RELATED TO CORNEAL SENSATION IN PATIENTS WITH DIABETES MELLITUS

	SENSATION		
	NORMAL	DECREASED	TOTAL
SCHIRMER TEST			
Normal	80/175	13/175	93
Decreased	63/175	19/175	82
Total	143	32	

de-sac and lid margins. Both anaerobic and aerobic bacterial cultures were obtained as well as cultures for mycotic organisms. In essence, our results show that bacterial flora of the conjunctiva is not significantly different than that reported for the normal population with respect to the types of bacteria present, however, we found that 94% of diabetic patients showed the presence of *Staphylococcus epidermidis* on the lid margins. There did not appear to be any correlation between the degree of metabolic control and the presence of staphylococcal organisms (Table X). With regard to anaerobic species and fungal species, diabetic patients revealed no unusual isolates (Tables X and XI).

Clinical examinations also included measurement of endothelial cell densities. This was prompted by previous reports that diabetic patients, following vitrectomy procedures, demonstrate persistent epithelial edema, delayed reepithelialization, and prolonged increases in corneal thickness measurements.⁹ These observations suggest an impairment of endothelial cell function which may or may not be reflected by endothelial cell counts, therefore, routine corneal pachymeter measurements were also obtained. Examinations performed during the second year of the study revealed that 38% of patients had corneal thickness measurements greater than 0.55 mm (Table VII). Endothelial cell counts were decreased in many patients but the cell densities were consistent with the ages of the patients being examined (Table XII).¹⁶

Electron microscope studies of eye bank eyes from diabetic and non-diabetic donors were done concurrently with the clinical examinations. None of these specimens were obtained from patients included in the clinical study. Microscopic examinations were confined to the corneal epithelium, basement membrane, and Bowman's membrane. Donor tissue from various age groups as well as tissue from nondiabetic donors was included to determine whether any observed changes were related specifically to diabetes. Initial examinations, which were limited to diabetic

TABLE X: CONJUNCTIVAL AND LID CULTURES IN PATIENTS WITH DIABETES MELLITUS ORGANISMS FOUND IN AEROBIC CULTURE PLATES

	GOOD CONTROL (25 pts., 50 eyes)		FAIR CONTROL (18 pts., 36 eyes)		POOR CONTROL (39 pts., 78 eyes)		TOTAL (82 pts., 164 eyes)	
	Lid	Conj.	Lid	Conj.	Lid	Conj.	Lid	Conj.
<i>Staphylococcus epidermidis</i>	48 (96%)	11 (22%)	34 (94.4%)	14 (38.9%)	73 (93.6%)	16 (20.5%)	155 (94.5%)	41 (2.5%)
<i>Corynebacterium</i> sp.	17 (34%)	9 (18%)	8 (27.7%)	5 (13.4%)	14 (17.9%)	10 (12.8%)	39 (23.8%)	24 (14.8%)
<i>Staphylococcus aureus</i>	3				8	1	11	1
<i>Proteus mirabilis</i>	1				2	2	3	2
<i>Flavobacterium</i> sp.					1		1	0
<i>Streptococcus mitis</i>					1		1	0
<i>Listeria monocytogenes</i>								
<i>Micrococcus</i>	2		2	2			2	2
<i>Alpha-strep viridans</i>	1		2	1			4	1
<i>Lactobacterium fermentum</i>			1				2	0
<i>Acinetobacter</i> species	2		1	1			1	1
<i>Pseudomonas cepacia</i>	3	1	1				3	1
TOTAL	77	21	49	23	99	29	225	73
Fungi								
<i>Cryptococcus</i>	2						2	0
<i>Candida</i> species		1					0	1
<i>Cladosporium</i> sp.					1		1	0
TOTAL	2	1	0	0	1	0	3	1

TABLE XI: CONJUNCTIVAL AND LID CULTURES IN PATIENTS WITH DIABETES MELLITUS ORGANISMS FOUND IN THIOGLYCOLLATE MEDIUM (ANAEROBIC)

	GOOD CONTROL (25 pts., 50 eyes)		FAIR CONTROL (18 pts., 36 eyes)		POOR CONTROL (39 pts., 78 eyes)		TOTAL (82 pts., 164 eyes)	
	Lid		Lid		Lid		Lid	
<i>Staphylococcus epidermidis</i>	27 (54%)		19 (52.8%)		41 (52.6%)		87 (53%)	
<i>Propionobacter</i> sp.	20 (40%)		7 (19.4%)		18 (23.1%)		45 (27.4%)	
<i>Staphylococcus aureus</i>					1		1	
<i>Bacillus</i> species				2	1		3	
<i>Proteus mirabilis</i>					4		4	
<i>Alpha-streptococcus viridans</i>	1						1	
<i>Clostridium perfringens</i>	1			1			2	
<i>Clostridium</i> species	2			1	1		4	
<i>Enterobacter aerogenes</i>				1			1	
<i>Lactobacterium fermentum</i>				1			1	
<i>Flavobacterium</i> species					2		2	
<i>Streptococcus faecalis</i>	1						1	
Non-hemolytic streptococcus	2						2	
TOTAL	54		32		68		154	

TABLE XII: MEASUREMENTS OF CORNEAL
ENDOTHELIAL CELL DENSITY IN PATIENTS WITH
DIABETES MELLITUS RELATED TO PATIENT AGE

AGE	ENDO. CELL DENSITY
17 - 19	3410 ± 186 (n=8)
20 - 29	3052 ± 328 (n=8)
30 - 39	2731 ± 348 (n=18)
40 - 49	2713 ± 318 (n=18)
50 - 59	2711 ± 302 (n=43)
60 - 60	2680 ± 366 (n=33)
70 +	2228 ± 650 (n=15)

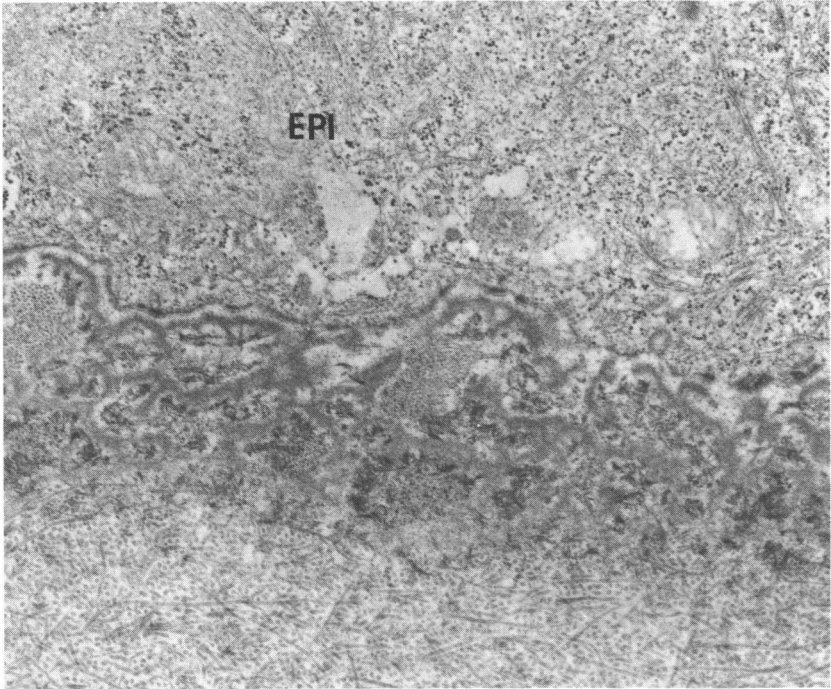


FIGURE 4

Multilaminar basement membrane underlying basal epithelial cell (EPI) in cornea from an 82-year-old donor who had been diabetic for five years. Electron dense filaments are also present in the thickened basement membrane (X23,000).

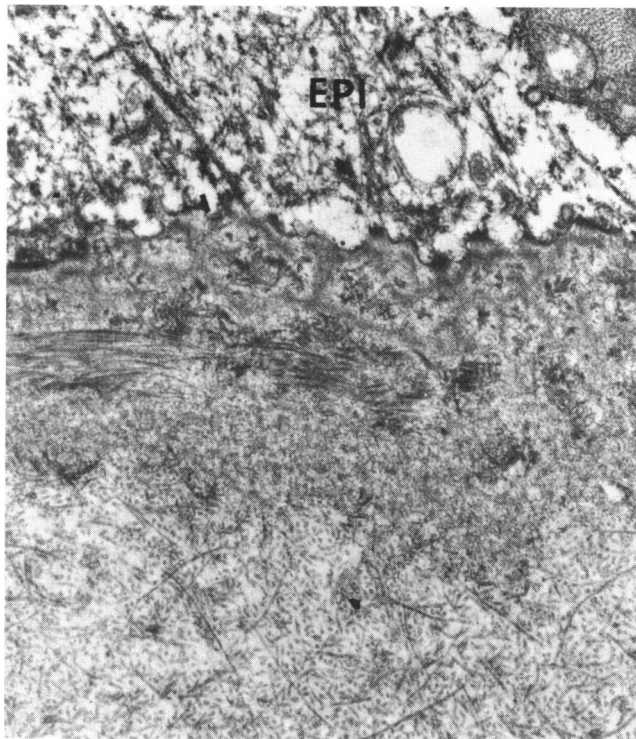


FIGURE 5

Similar multilaminar basement membrane containing electron dense filaments in a cornea from an 80-year-old donor with no history of diabetes or recognized corneal abnormalities. The epithelial cell (EPI) is edematous due to eye bank storage (X23,000).

tissue from 15 patients, revealed multilaminar, irregular, and thickened basement membranes, as illustrated in Figure 4. We explored this further to determine if prolonged time between death and tissue fixation might produce the observed changes. Multilaminar basement membranes were found in corneas fixed as quickly as six hours after death, as well as those fixed up to 60 hours post mortem. Enucleated eyes from ten nondiabetic patients in comparable age groups were then examined to determine whether these changes were specific for diabetes. Electron microscopy revealed that discontinuities and a multilaminar structure of basement membrane could be found in nondiabetic corneas. Figure 5 illustrates the presence of a multilaminar basement membrane and accumulation of wide-banded collagen with electron dense material anterior to Bowman's

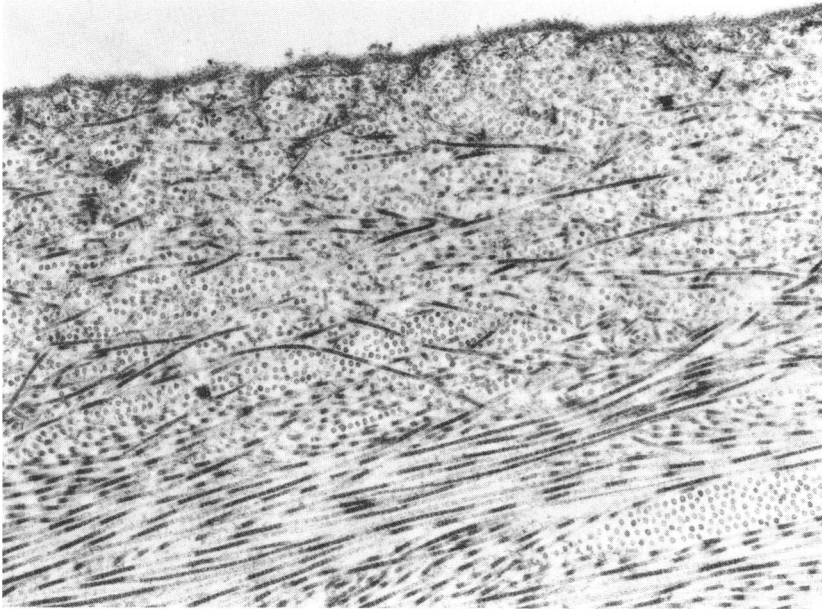


FIGURE 6

Intact basement membrane in a normal rabbit cornea 24 hours after transcorneal freezing. A brass probe cooled in liquid nitrogen was used to destroy corneal epithelial and endothelial cells (X22,000).

membrane in an age-matched nondiabetic patient. These alterations are, therefore, either a variation of normal or possibly related to age, but in any event they do not appear to be specific for patients with diabetes mellitus.¹⁷

In an effort to determine whether corneal and anterior segment abnormalities in diabetic patients are associated with genetic markers, we performed HLA typing on the serum of this patient population. Final results of this work will be published separately but preliminary results indicate there is no significant correlation between corneal pathology and HLA types. We do not have sufficient information at the present time, however, to rule out correlation with clinical subgroups. The loci being examined are A, B, W₄/W₆, C, D_R, MB, MT.

SUMMARY AND DISCUSSION

It appears that clinical abnormalities of the diabetic cornea consist of the following: 47% to 64% of patients demonstrate epithelial lesions at any

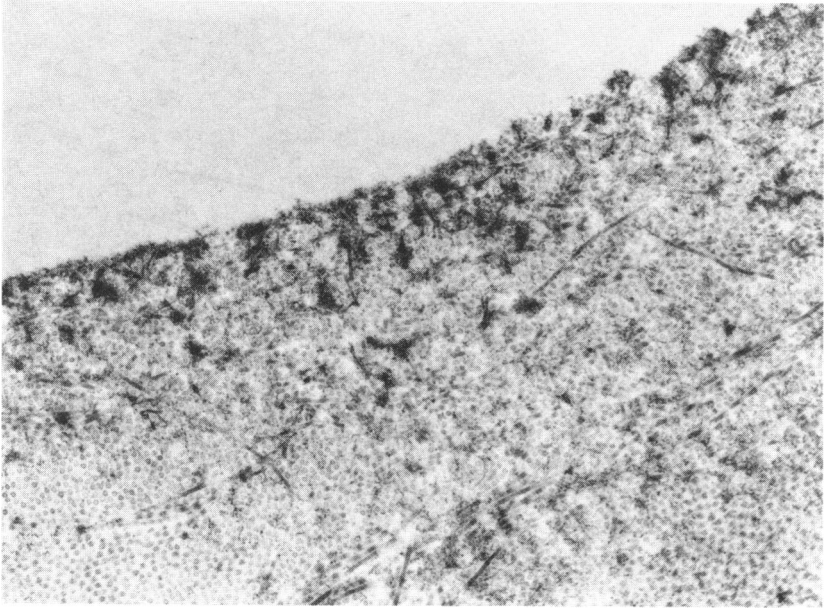


FIGURE 7

Anterior surface of a cornea from an alloxan induced diabetic rabbit 24 hours after transcorneal freezing. The basement membrane was apparently removed along with the epithelial cells (X22,000).

given time; corneal sensation is reduced in 18% of patients; 47% of the patients in this study showed decreased tear production; 94% of all patients showed the presence of *Staphylococcus epidermidis* on the lid margin. In addition, we have noted corneal thickness measurements which exceed 0.55 mm in 38% of patients and while endothelial cell densities were reduced in this patient population, the reductions appear to be related to age rather than the presence of diabetes. The epithelial keratopathy associated with diabetes might be due to factors of diminished corneal sensation and reduced tear production combined with the presence of *Staphylococcus epidermidis* on the lid margin, however, present statistical data are not adequate to prove this. In any event, our clinical examinations have not provided a clear explanation for the observed fragility of corneal epithelium noted during surgical procedures and the recurrent erosion syndromes noticed postoperatively or following other forms of trauma. Furthermore, electron microscopic studies of diabetic corneas failed to confirm a specific structural defect in the epithe-

lial basement membrane of the normal or nontraumatized diabetic patient. Current laboratory studies may provide information, however, to explain some of these observations.

Electron microscopic studies in alloxan induced diabetic rabbits show that damage to the corneal epithelium, produced by freezing, removes the basement membrane as well as epithelium.¹⁸ The absence of a basement membrane following trauma would obviously affect both regeneration of epithelium and the adherence of regenerated epithelium. The removal of basement membrane following freeze induced injury to the cornea (Fig 5) does not occur in nondiabetic animals (Fig 6). If a similar process occurs in humans following nonspecific injury to the corneal epithelium, this might provide an explanation for the delay in epithelial regeneration and poor adhesion of this tissue following surgical trauma.

Additional laboratory data which may be pertinent to epithelial defects relate to the presence of sorbitol and other sugars in the corneal epithelium. Friend¹⁹ has reported the presence of a sorbitol pathway in normal corneal epithelium which can be activated in the presence of high levels of intracellular glucose. This author indicates further that corneal epithelium is an insulin insensitive tissue. Based on her experimental work, she concluded, however, that the low levels of sorbitol which can accumulate would be insufficient to cause profound osmotic imbalance within the epithelial cells. Our current laboratory studies in diabetic humans indicate that significant amounts of glucose, fructose, and sorbitol, along with two other unidentified sugars, are present in the corneal epithelium of diabetic patients and are not present in nondiabetic patients.²⁰ The significance of this observation with regard to the pathophysiology of corneal disease is speculative, but it is possible that intracellular accumulations of sorbitol in sufficient quantities could produce overhydration of epithelial cells. Fukushi's²¹ recent work shows that aldose reductase inhibitors enhance epithelial regeneration in diabetic rats and also preserved corneal transparency after resurfacing had been completed. This also suggests that sorbitol accumulation in corneal epithelium may, indeed, have clinical significance with respect to the various forms of keratopathy seen in diabetic patients.

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DISCUSSION

DR FRANK W. NEWELL. A number of factors must be considered in any study of diabetic patients: whether the diabetes is insulin-dependent or not, the duration of the disease, the adequacy of the control of the diabetes, and the severity of other complications. It is important to determine whether changes observed are the result of the diabetes itself, are caused by another disorder, or are age-related.

Doctor Schultz and his coworkers studied patients from a metabolic clinic who did not have ocular disease and symptoms and found keratopathy in 56 of 120 patients examined the first year and in 50 of 89 of the same patients examined the second year. There was no mention of the rate of blinking, abnormalities of the preocular tear film, lid abnormalities, or other common causes of epithelial changes in an elderly group. The keratopathy was not correlated with the decreased tear production, reduced corneal sensitivity, or *Staphylococcus*. Whether or not this is a rate in excess of normal is not known inasmuch as only diabetics are described.

Olson, Busted, and Schmitz (*Lancet* 1:883, 1980) described the cornea as being thicker in patients with insulin-dependent diabetes who had proliferative retinopathy. They found no correlation with the duration of diabetes or the fasting blood glucose.

Pardos and Krachmer (*Am J Ophthalmol* 90:172, 1980) found no difference between the diabetic and control population in endothelial cell count. Patients with diabetes aged 70 to 79 years had a decreased number of cells.

With respect to poor wound healing and diabetes and the susceptibility to infection, we must recall that many of these observations were made before the advent of insulin and careful control of diabetes. Recently, Snip, Thoft, and Tolentino (*Am J Ophthalmol* 90:463 1980) studied 27 patients with retinal detachment who had undergone a pars plana vitrectomy with or without a scleral buckling procedure. There were 14 diabetic and 13 nondiabetic subjects who showed similar rates of epithelial healing in the normal cornea.

Corneal sensation decreases with age even in the absence of diabetic keratopathy, and Jordan and Baum (*Ophthalmology* 87:920, 1980) showed an absent blink reflex in 24% of the elderly.

I thought one of the most interesting aspects of the present study was the demonstration that the abnormalities observed previously in the basement membrane of the corneal epithelium were caused by artifactual changes occurring after death and did not indicate a generalized thickening of the basement membrane. Additionally, studies in progress suggest no correlation between the keratopathy and genetic markers relating to histocompatibility complex as indicated by HL-A typing.

Doctor Schultz's interest in the sorbitol pathway is of interest. As far as I can determine, every cell that metabolizes sugar also has a sorbitol pathway. It is of minor importance and is active only when an excess of glucose is present. Possibly this pathway is important in vascular cells too and would account for major complications.

DR JOHN C. LOCKE. I enjoyed Doctor Schultz' paper very much. I have an experience to relate that I think may be relevant. Some years ago in the course of doing some Xenon arc photocoagulation for diabetic retinopathy, for reasons that I never understood, a few of my patients would develop severe pain in and around the eye after the retrobulbar injection wore off. This only lasted a few hours so I thought it might be helpful to use bupivacaine (Marcaine) in the retrobulbar injection. As taught by Doctor Meyer-Schwickerath, our retrobulbar injection consisted of 4, 4.5 or 5 ml so I gave a retrobulbar injection containing half 0.75% Marcaine and half 0.5% lidocaine (Xylocaine). I treated ten cases in this way and five of them developed a severe form of what I diagnosed as neurotrophic keratitis which lasted several days to weeks. On examination there was a diffuse epithelial haze, there was a dry eye and there was reduced sensitivity of the corneas that Doctor Schultz has just described. One was severe enough that we had to put in lid adhesions and maintain them to this day. In another case, I treated proliferative diabetic retinopathy with diathermy as recommended by the Amalric-

Wessing procedure 180 degrees around the globe. I did this under local anesthesia and again used Marcaine and again had a keratitis which lasted for a few weeks postoperatively, so I concluded that there was, in fact, a neuropathy of the sensory nerve supply to the cornea of these diabetics which I feel was precipitated by using this long-acting regional anesthetic. I use Marcaine when I do intraocular lens surgery in diabetics. I have never had this experience in photocoagulation when I use Xylocaine alone and I'll never use Marcaine again. I would like to ask Doctor Schultz if he thinks that some of the changes he described are perhaps manifestations of a diabetic neuropathy of the sensory nerve supply to the cornea.

DR MAX FORBES. I would like to congratulate Doctor Schultz on a very interesting study. I wonder if he could comment on the question of contact lens wear in diabetics because many of our cataract patients have diabetes. If they do have this corneal epithelial problem that has been described, it would seem to me that they should have an increased incidence of problems in wearing contact lenses after cataract surgery. I would like to know if Doctor Schultz has any experience in this area.

DR PETER LABISON. Doctor Schultz, I would like to explore just a little further the changes you saw in the basement membrane in the postmortem eyes. Did you feel the basement membrane was abnormal because of postmortem changes or from the diabetic retinopathy? Doctor William Tasman at Wills Eye Hospital has done a number of panretinal photocoagulations and has asked us to put soft lenses on these eyes because of the frequency of recurrent corneal erosions afterward. It seems as if the patients that have used soft contact lenses OU prior to panretinal photocoagulation were not getting the high incidence of recurrent erosions.

DR RICHARD O. SCHULTZ. Thank you Doctor Newell, for your discussion. I will try to respond to some of your questions: The presence of epithelial keratopathy in these patients was more common in the adult onset group; and the average age of patients was greater in this group. If one combines the juvenile and adult onset groups, there were equivalent percentages of involved individuals in both sexes. Your second question asked whether the 89 patients examined in the second year of the study were the same patients examined in the first year. Yes, they were. Eighty-nine of the original 120 patients appeared for re-examination the second year.

One of the important points raised in your discussion relates to the possible association between epithelial lesions, decreased tear production, reduced corneal sensation, and the presence of *staphylococcus epidermidis* on the lid margins. Epithelial lesions in these patients might be related to all three factors, but our present statistical data are not adequate to prove this. If the lesions were due to the presence of staphylococci, I would expect these patients to be symptomatic, which they were not. With regard to the comment that early reports of keratopathy in diabetics were made prior to the availability of insulin; this does not necessarily mean that corneal epithelial lesions were related to poor diabetic

control. Our data, in fact, indicates that keratopathy is not related to the degree of diabetic control.

Two of the discussers commented about postmortem changes in the electron microscopic studies of the epithelial basement membrane. We do not believe that these are postmortem changes or that they are artifacts of fixation. Thickened and multilaminar basement membranes were found in age-matched nondiabetic patients as well as diabetic patients. Thus, these changes are not specific for diabetes. These changes were also found in corneas fixed as early as six hours after death as well as those fixed 60 hours postmortem. Therefore, the changes are probably not due to postmortem autolysis. It would appear that these basement membrane changes are age related but in any event they are not due specifically to the presence of diabetes.

Doctor Newell commented that sorbitol can be found in any tissue where glucose is present in excess amounts. This statement is correct, but in the non-diabetic patient, free glucose is not normally present in the corneal epithelium. The fact that we have found sorbitol and other sugars in the corneal epithelium of diabetic patients indicates that glucose is present in excess amounts in this tissue and I think this is very significant.

Doctor Locke asked about the presence of peripheral neuropathy in these patients. We did perform general neurologic examinations and there is evidence to suggest that decreased corneal sensation in diabetic patients is part of the generalized polyneuropathy. With regard to the question of diabetic patients wearing contact lenses, I would be cautious about this because of decreased corneal sensation and tear production; and would suggest close observation of these patients.

Doctor Laibson asked whether tissue specimens showing basement membrane changes, demonstrated any associated pathology in the epithelium. I do not think so, but I cannot answer that question for certain without re-examination of the tissue.